

ORIGINAL ARTICLE

Tranexamic Acid for the Prevention of Blood Loss after Cesarean Delivery

L. Sentilhes, M.V. Sénat, M. Le Lous, N. Winer, P. Rozenberg, G. Kayem, E. Verspyck, F. Fuchs, E. Azria, D. Gallot, D. Korb, R. Desbrière, C. Le Ray, C. Chauleur, F. de Marcillac, F. Perrotin, O. Parant, L.J. Salomon, E. Gauchotte, F. Bretelle, N. Sananès, C. Bohec, N. Mottet, G. Legendre, V. Letouzey, B. Haddad, D. Vardon, H. Madar, A. Mattuizzi, V. Daniel, S. Regueme, C. Roussillon, A. Benard, A. Georget, A. Darsonval, and C. Deneux-Tharoux, for the Groupe de Recherche en Obstétrique et Gynécologie*

ABSTRACT

BACKGROUND

Prophylactic administration of tranexamic acid has been associated with reduced postpartum blood loss after cesarean delivery in several small trials, but evidence of its benefit in this clinical context remains inconclusive.

METHODS

In a multicenter, double-blind, randomized, controlled trial, we assigned women undergoing cesarean delivery before or during labor at 34 or more gestational weeks to receive an intravenously administered prophylactic uterotonic agent and either tranexamic acid (1 g) or placebo. The primary outcome was postpartum hemorrhage, defined as a calculated estimated blood loss greater than 1000 ml or receipt of a red-cell transfusion within 2 days after delivery. Secondary outcomes included gravimetrically estimated blood loss, provider-assessed clinically significant postpartum hemorrhage, use of additional uterotonic agents, and postpartum blood transfusion.

RESULTS

Of the 4551 women who underwent randomization, 4431 underwent cesarean delivery, 4153 (93.7%) of whom had primary outcome data available. The primary outcome occurred in 556 of 2086 women (26.7%) in the tranexamic acid group and in 653 of 2067 (31.6%) in the placebo group (adjusted risk ratio, 0.84; 95% confidence interval [CI], 0.75 to 0.94; $P=0.003$). There were no significant between-group differences in mean gravimetrically estimated blood loss or in the percentage of women with provider-assessed clinically significant postpartum hemorrhage, use of additional uterotonic agents, or postpartum blood transfusion. Thromboembolic events in the 3 months after delivery occurred in 0.4% of women (8 of 2049) who received tranexamic acid and in 0.1% of women (2 of 2056) who received placebo (adjusted risk ratio, 4.01; 95% CI, 0.85 to 18.92; $P=0.08$).

CONCLUSIONS

Among women who underwent cesarean delivery and received prophylactic uterotonic agents, tranexamic acid treatment resulted in a significantly lower incidence of calculated estimated blood loss greater than 1000 ml or red-cell transfusion by day 2 than placebo, but it did not result in a lower incidence of hemorrhage-related secondary clinical outcomes. (Funded by the French Ministry of Health; TRAAP2 ClinicalTrials.gov number, NCT03431805.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sentilhes at the Department of Obstetrics and Gynecology, Bordeaux University Hospital, Place Amélie Raba Léon, 33076 Bordeaux, France, or at loicsentilhes@hotmail.com.

*A list of the members and collaborators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Sénat and Le Lous contributed equally to this article.

N Engl J Med 2021;384:1623-34.

DOI: 10.1056/NEJMoa2028788

Copyright © 2021 Massachusetts Medical Society.



A Quick Take
is available at
NEJM.org

POSTPARTUM HEMORRHAGE REMAINS A leading cause of severe maternal complications and death worldwide.¹ Prophylactic administration of a uterotonic agent is recommended to reduce the risk of postpartum hemorrhage.²⁻⁴ Tranexamic acid has emerged in the past decade as another candidate drug to prevent blood loss after childbirth. Tranexamic acid has antifibrinolytic effects that are achieved at least in part by promotion of hemostasis through the blocking of lysine-binding sites on plasminogen molecules, and evidence of its clinical effects has been found in various contexts.^{5,6} In clinical trials outside of obstetrics, tranexamic acid has been found to reduce the need for transfusions in elective surgery^{7,8} and to reduce mortality among patients with extracranial⁹ or mild-to-moderate intracranial trauma.¹⁰

Tranexamic acid also reduces bleeding-related mortality among women with postpartum hemorrhage¹¹ and is consequently recommended worldwide for these patients.^{12,13} Moreover, the survival benefit associated with the earlier administration of the drug in these women¹⁴ suggests that it may prevent coagulopathy after delivery rather than treat it.^{4,6,14}

We examined the effect of prophylactic tranexamic acid at vaginal delivery in a previous trial published in the *Journal* and found no significant effect on the incidence of blood loss of at least 500 ml in women who also received a prophylactic uterotonic agent.¹⁵ Small, single-center, randomized, controlled trials have shown significantly reduced blood loss when prophylactic tranexamic acid is given to women undergoing elective cesarean delivery.⁴⁻⁶ Nevertheless, because of methodologic limitations related to blinding, outcome assessment, attrition bias, and absence of postdischarge follow-up, especially for thromboembolic events, the findings in these trials are interpreted as inconclusive,^{4-6,16,17} and current guidelines do not advocate routine administration of tranexamic acid after cesarean deliveries.^{4,13} We designed this trial to investigate whether tranexamic acid plus a prophylactic uterotonic agent would be associated with a lower incidence of postpartum hemorrhage after cesarean delivery than the uterotonic agent alone.

METHODS

TRIAL DESIGN

We conducted the Tranexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean

Delivery (TRAAP2) trial, a multicenter, randomized, placebo-controlled, double-blind trial with two parallel groups that was modeled on our previous trial of tranexamic acid after vaginal delivery (TRAAP trial).^{15,18} Women who were expected to undergo a cesarean delivery were randomly assigned to receive a uterotonic agent plus either tranexamic acid or placebo immediately after delivery. Details of the rationale and design of the trial have previously been published,¹⁹ and the protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

The trial protocol was approved by the Northwest VI Committee for the Protection of Research Subjects and the French National Agency of Medicine and Health Products Safety. The first, last, and fourth-to-last authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol and statistical analysis plan. No company or manufacturer was involved in the trial.

PARTICIPANTS

Women were eligible to participate if they were 18 years of age or older with a singleton or multiple pregnancy at 34 or more weeks of gestation and were expected to undergo cesarean delivery before or during labor. They were recruited at 27 French maternity hospitals. Women with a known or possible increased risk of venous or arterial thrombosis or of bleeding, a history of epilepsy or seizure, a prenatal hemoglobin level of 9 g per deciliter or lower in the week before delivery, or poor comprehension of spoken French were not eligible (details of the exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org).¹⁹ Caregivers (physicians or midwives) provided information about the trial individually to each woman during late pregnancy. Women confirmed participation and provided written informed consent only if the investigator considered cesarean delivery to be likely.

RANDOMIZATION AND PROCEDURES

Eligible women who had provided consent were randomly assigned in a 1:1 ratio to receive either 1 g of tranexamic acid (purchased at full cost from Sanofi Aventis) or placebo (normal saline, Fresenius Kabi). Computerized randomization (in blocks of four) was performed centrally through a secure Internet facility (Ennov Clinical Software) and was stratified according to trial site and timing of cesarean delivery (before or

during labor). The randomization procedure was supervised at Bordeaux University Hospital, and information on each randomization was transmitted to the PPRIGO (Production Pharmaceutique pour la Recherche Institutionnelle du Grand Ouest) hospital pharmacists' consortium, which prepared the ampules of tranexamic acid or placebo. The products were prepared in numbered and labeled boxes, each containing a 10-ml vial of either tranexamic acid (1 g) or placebo, depending on the randomization number. All boxes and vials were identically labeled and were differentiated only by their randomization numbers. Neither the participants nor the investigators were aware of the group assignments during the trial.

Clinicians were instructed to administer tranexamic acid or placebo intravenously over a period of 30 to 60 seconds during the 3 minutes after birth, after the prophylactic uterotonic agent (5 or 10 IU of oxytocin or 100 μ g of carbetocin) had been administered and the cord had been clamped. Administration of the prophylactic uterotonic agent (and tranexamic acid or placebo) may have been followed by a 2-hour oxytocin infusion, in accordance with the policy at each center. All these aspects of management of the third stage of labor were standardized at each center and adhered to national guidelines, including the possibility of administering tranexamic acid if postpartum hemorrhage occurred.²⁰

After cesarean delivery, women were transferred from the operating room to the postanesthesia care unit (PACU), where they stayed for at least 2 hours, until the birth attendant considered that bleeding had diminished to the normally expected amount. Gravimetrically estimated blood loss was assessed. A venous blood sample was obtained on day 2 after delivery for outcome assessment. Adverse events were assessed until hospital discharge and by telephone interview at 3 months after delivery, given the increased thromboembolic risk during the 3-month period after delivery.²¹

OUTCOMES

The primary outcome was postpartum hemorrhage, defined as a calculated estimated blood loss greater than 1000 ml or a red-cell transfusion within 2 days after delivery.²² The estimated blood loss was calculated as the estimated blood volume \times (preoperative hematocrit $-$ postoperative hematocrit) \div preoperative hematocrit; the estimated blood volume in milliliters was calculated as

the body weight in kilograms \times 85.²²⁻²⁵ We chose this quantitative objective estimate of blood loss because of the limited accuracy of blood-loss estimation for cesarean deliveries when other, subjective methods are used.²⁰ Preoperative hematocrit was the value most recently measured within 8 days before delivery, and postoperative hematocrit was that measured closest to day 2 after delivery (without transfusion).

Secondary outcomes included clinical and laboratory (blood samples at day 2) measurements of postpartum blood loss,²⁶⁻²⁸ adverse events that were assessed by the investigators as being potentially related to tranexamic acid, maternal satisfaction on day 2, and psychological status at 2 months, assessed with the Edinburgh Postnatal Depression Scale (EPDS).²⁹ These secondary outcomes belong to the consensus core outcome set for studies evaluating interventions for the prevention and treatment of postpartum hemorrhage³⁰ and are described in detail in Table S2.¹⁹

The physician responsible for the delivery prospectively recorded the procedures used during the third stage of labor and clinical outcomes identified in the immediate postpartum period. Research assistants who were independent of the local medical team obtained all other data from medical charts.

STATISTICAL ANALYSIS

We based the expected incidence of the primary outcome on results in the placebo group in previous studies,^{22,31} in particular the Elective Cesarean Section Syntocinon (oxytocin) Infusion Trial (ECSSIT),²² and estimated that 4072 women undergoing cesarean delivery would provide power of at least 80% to detect a relative difference of 20% or greater in the incidence of the primary outcome (i.e., 15% in the placebo group and 12% in the tranexamic acid group), with a 5% two-sided type I error. Given the expected percentage of women who would deliver vaginally, be lost to follow-up, or lack the blood samples needed for the assessment of the primary outcome (estimated at a maximum of 10%), we aimed to enroll 4524 women in order to include the needed number of women undergoing a cesarean delivery with available data for assessment of the primary outcome.

The main analysis of the primary and secondary outcomes was performed in the modified intention-to-treat population, which included all women who underwent randomization and had

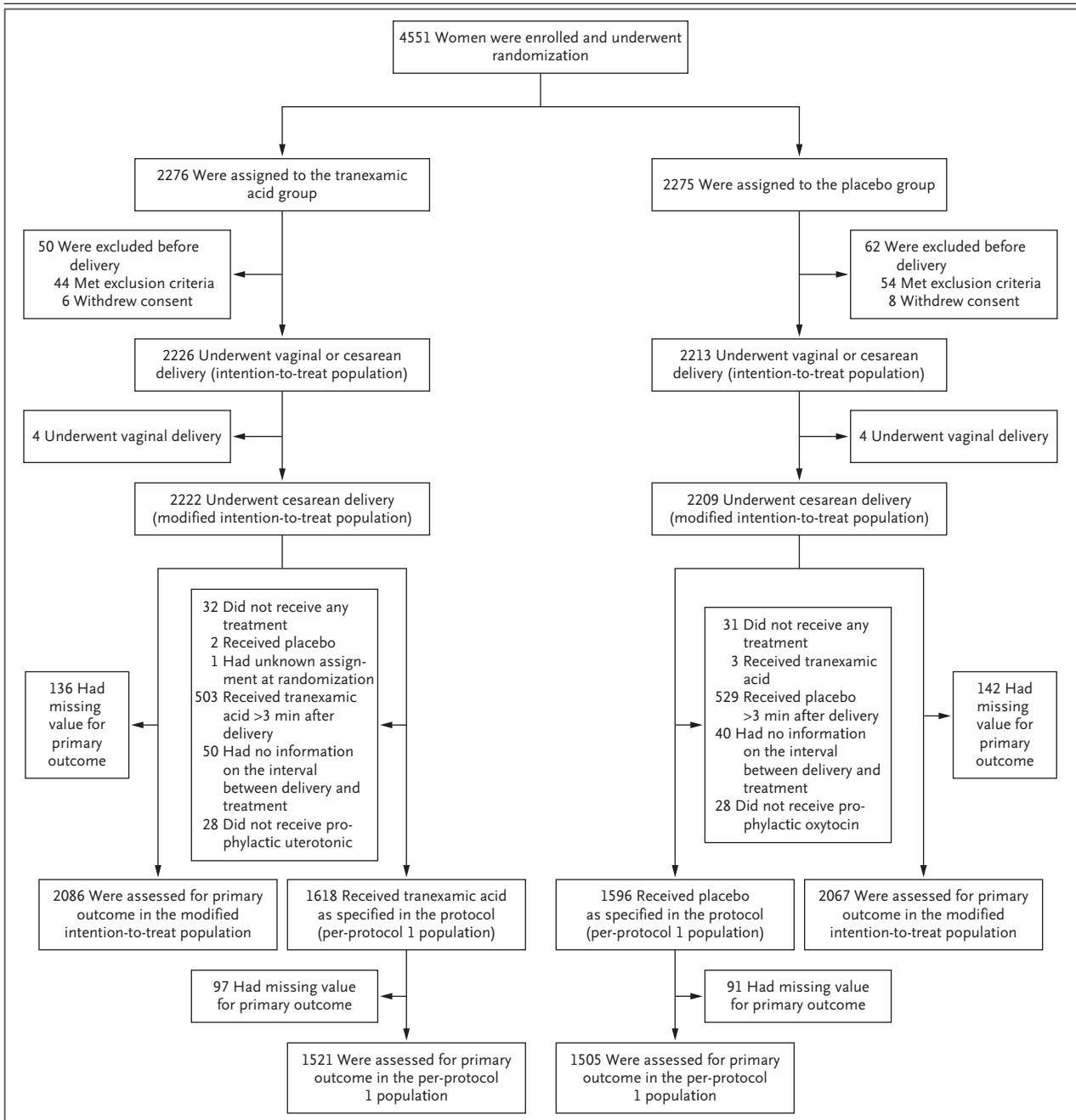


Figure 1. Randomization and Treatment.

Patients who had missing values for the primary outcome were those for whom data on preoperative hematocrit, postoperative hematocrit, or maternal weight were not available. The per-protocol 1 population included women in the modified intention-to-treat population who received oxytocin and then either tranexamic acid or placebo within 3 minutes after giving birth.

a cesarean delivery, with the exception of those who withdrew consent or were determined to be ineligible after randomization. The safety population included all women who received tranexamic acid or placebo. We also analyzed two per-protocol populations, which included women

from the modified intention-to-treat population who received a uterotonic agent and then tranexamic acid or placebo within 3 minutes after birth (per-protocol 1 population) or within 10 minutes after birth (per-protocol 2 population), as prespecified in the protocol; the latter situ-

Table 1. Characteristics of Participants at Baseline and Management of the Third Stage of Labor (Modified Intention-to-Treat Population).*

Characteristic	Tranexamic Acid Group (N = 2222)	Placebo Group (N = 2209)
Age — yr	33.3±5.3	33.5±5.3
Body-mass index before pregnancy†	26.3±6.4	26.1±6.2
Primiparous — no./total no. (%)	826/2222 (37.2)	808/2207 (36.6)
Previous cesarean delivery — no./total no. (%)	1151/2221 (51.8)	1155/2203 (52.4)
One previous cesarean delivery	633/2221 (28.5)	663/2203 (30.1)
At least two previous cesarean deliveries	518/2221 (23.3)	492/2203 (22.3)
History of postpartum hemorrhage — no./total no. (%)	114/2221 (5.1)	99/2203 (4.5)
Multiple pregnancy — no. (%)	160 (7.2)	159 (7.2)
Gestational diabetes — no./total no. (%)	470/2220 (21.2)	476/2207 (21.6)
Gestational hypertensive disorders — no./total no. (%)	141/2220 (6.4)	142/2207 (6.4)
Hospitalization >24 hr during pregnancy — no./total no. (%)	282/2220 (12.7)	258/2207 (11.7)
Median gestational age at delivery (IQR) — wk	39 (38–40)	39 (38–40)
Timing of cesarean delivery — no. (%)		
Before labor	1580 (71.1)	1565 (70.8)
During labor	642 (28.9)	644 (29.2)
Median duration of cesarean delivery (IQR) — min	36 (30–45)	37 (29–46)
Epidural or spinal anesthesia — no./total no. (%)	2199/2213 (99.4)	2183/2202 (99.1)
General anesthesia — no./total no. (%)	66/2186 (3.0)	84/2182 (3.8)
Induction of labor — no./total no. (%)	312/2214 (14.1)	317/2203 (14.4)
Oxytocin during labor — no./total no. (%)	479/2209 (21.7)	500/2197 (22.8)
Prophylactic uterotonic agent at birth — no./total no. (%)	2194/2218 (98.9)	2181/2204 (99.0)
Prophylactic carbetocin at birth	905/2218 (40.8)	888/2204 (40.3)
Prophylactic oxytocin at birth	1295/2218 (58.4)	1299/2204 (58.9)
Median interval between delivery and administration of tranexamic acid or placebo (IQR) — min	2 (1–3)	2 (1–3)
Controlled cord traction — no./total no. (%)	1355/1998 (67.8)	1374/1991 (69.0)
Anticoagulant prophylaxis after delivery — no./total no. (%)	1296/2203 (58.8)	1296/2193 (59.1)

* Plus–minus values are means ±SD. Data on age were missing for 2 women in the tranexamic group and for 3 women in the placebo group; on body-mass index for 38 and 43, respectively; on duration of cesarean delivery for 127 and 146, respectively; and on interval between delivery and administration of tranexamic acid or placebo for 83 and 71, respectively. IQR denotes interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

ation is more consistent with routine clinical practice.¹⁹

The primary outcome analysis was conducted with multiple imputation by fully conditional specification to take missing values into account. We performed sensitivity analyses of the primary outcome first by imputing missing values as failures and then by using complete cases. Secondary analyses were conducted with available data.

Participants' baseline characteristics, management of the third stage of labor, and protocol adherence are provided as descriptive data: qualitative variables are expressed as percentages and

quantitative variables as either means with standard deviations or medians with interquartile ranges, as appropriate. The effects of tranexamic acid are expressed as risk ratios with 95% confidence intervals for categorical outcomes estimated with Poisson mixed-effects models and as mean differences with 95% confidence intervals for quantitative outcomes estimated with linear mixed-effects models; all models were adjusted for center and timing of cesarean delivery (before or during labor).¹⁹

Two prespecified subgroup analyses were used to test the effect of tranexamic acid on the

Table 2. Primary and Secondary Outcomes in the Modified Intention-to-Treat Population.*

Outcome	Tranexamic Acid Group (N = 2222)	Placebo Group (N = 2209)	Unadjusted Difference (95% CI) ^{††}	Adjusted Risk Ratio or Mean Difference (95% CI) ^{‡‡}	P Value ^{§§}
Postpartum hemorrhage — no./total no. (%)¶	556/2086 (26.7)	653/2067 (31.6)	-4.9 (-7.7 to -2.2)	0.84 (0.75 to 0.94)	0.003
Calculated estimated blood loss >1000 ml	550/2084 (26.4)	650/2066 (31.5)	-5.1 (-7.8 to -2.3)	0.84 (0.75 to 0.94)	—
Red-cell transfusion by day 2	35/2221 (1.6)	30/2209 (1.4)	0.2 (-0.5 to 0.9)	1.16 (0.71 to 1.89)	—
Gravimetrically estimated blood loss — ml	689±887	719±920	-30.6 (-90.2 to 29.0)	-33.06 (-77.48 to 11.37)	NS
Gravimetrically estimated blood-loss category — no./total no. (%)					
>500 ml	1133/1774 (63.9)	1110/1754 (63.3)	0.6 (-2.6 to 3.8)	1.01 (0.93 to 1.09)	—
>1000 ml	545/1774 (30.7)	521/1754 (29.7)	1 (-2 to 4)	1.03 (0.92 to 1.16)	—
Clinically significant postpartum hemorrhage according to health care providers — no./total no. (%)	303/2220 (13.6)	327/2208 (14.8)	-1.2 (-3.2 to 0.9)	0.92 (0.79 to 1.08)	NS
Additional uterotonic agents for excessive bleeding — no./total no. (%)	130/2217 (5.9)	159/2206 (7.2)	-1.3 (-2.8 to 0.1)	0.81 (0.64 to 1.03)	NS
Blood transfusion — no./total no. (%)	42/2221 (1.9)	39/2208 (1.8)	0.1 (-0.7 to 0.9)	1.07 (0.69 to 1.66)	NS
No. of red-cell units transfused	3.1±1.9	3.2±2.2	-0.1 (-1.0 to -0.08)	-0.08 (-1.18 to 1.01)	—
Postoperative iron sucrose infusion — no./total no. (%)	60/2196 (2.7)	44/2185 (2.0)	0.7 (-0.2 to 1.6)	1.35 (0.91 to 1.99)	—
Arterial embolization, emergency surgery for postpartum hemorrhage, or hysterectomy — no./total no. (%)**	13/2221 (0.6)	7/2209 (0.3)	0.3 (-0.1 to 0.7)	1.84 (0.73 to 4.62)	NS
Transfer to intensive care unit — no./total no. (%)	32/2221 (1.4)	22/2209 (1.0)	0.4 (-0.2 to 1.1)	1.44 (0.83 to 2.47)	—
Calculated estimated blood loss — ml ^{††}	680±748	787±750	-107 (-152 to -61)	-107 (-152 to -63)	<0.001
Calculated estimated blood loss category — no./total no. (%) ^{††}					
>500 ml	1213/2084 (58.2)	1326/2066 (64.2)	-6.0 (-8.9 to -3.0)	0.91 (0.84 to 0.98)	—
>1500 ml	215/2084 (10.3)	263/2066 (12.7)	-2.4 (-4.4 to -0.5)	0.81 (0.68 to 0.97)	—
Hemoglobin ^{‡‡}					
Peripartum change — g/dl	-1.2±1.2	-1.4±1.2	0.2 (0.1 to 0.3)	0.18 (0.11 to 0.25)	<0.001
Peripartum decrease >2 g/dl — no./total no. (%)	397/2088 (19.0)	497/2071 (24.0)	-5.0 (-7.5 to -2.5)	0.79 (0.69 to 0.90)	—
Hematocrit ^{††}					
Peripartum change — percentage points	-3.5±3.7	-4.0±3.7	0.5 (0.3 to 0.8)	0.53 (0.31 to 0.75)	<0.001
Peripartum decrease >10 percentage points — no./total no. (%)	66/2086 (3.2)	93/2071 (4.5)	-1.3 (-2.5 to -0.2)	0.70 (0.51 to 0.97)	—

* Plus-minus values are means ±SD. No hypovolemic shock or maternal death occurred in either group. Data on gravimetrically estimated blood loss were not available for 448 women in the tranexamic acid group and 455 in the placebo group; on red-cell units transfused for 2180 and 2170, respectively; on calculated estimated blood loss for 138 and 143, respectively; on peripartum change in hemoglobin level for 134 and 138, respectively; and on peripartum change in hematocrit for 136 and 138, respectively. NS denotes not significant (in accordance with the Benjamini-Hochberg procedure).

† Differences between the groups are given in percentage points, and differences between mean values in the units of the mean values.

‡ Adjusted risk ratios and adjusted mean differences were estimated with the use of Poisson mixed-effects regression models and linear mixed-effects models, respectively, with systematic adjustment for randomization stratification variables (center and timing of cesarean delivery [before or during labor]). For the primary outcome, missing data were imputed with the PROC-MI fully conditional specification method in SAS; imputation was conditional on center, timing of the cesarean, body-mass index before pregnancy, age, gestational age at delivery, pregnancy-related disorder (preexisting chronic hypertension, gestational hypertensive disorders, preexisting diabetes mellitus, gestational diabetes, or hospitalization >24 hours during pregnancy), multiple pregnancy, primiparity, geographic origin, and notable obstetrical history (uterine scar, previous cesarean delivery, or previous postpartum hemorrhage).

§ With the exception of the primary outcome, for which the P value was unadjusted, all P values were adjusted for multiple testing with the use of the Benjamini–Hochberg procedure; the secondary outcomes are listed in a logical order for clinicians and not in the order of the P values obtained through the Benjamini–Hochberg procedure. No P values are provided for outcomes for which the difference was not tested in accordance with the statistical analysis plan (details are provided in Table S6).

¶ Postpartum hemorrhage was defined as a calculated estimated blood loss of greater than 1000 ml or receipt of a red-cell transfusion within 2 days after delivery.

|| Gravimetrically estimated blood loss was assessed by measuring the suction volume and swab weight from, among other items, disposable waterproof drapes with pockets that captured blood and amniotic fluid. Only data for women enrolled on or after August 7, 2018, are considered (data monitoring before that date showed a lack of reliability).

** In the tranexamic acid group, 4 women underwent arterial embolization, 7 a uterus-sparing surgical procedure (vessel ligation or uterine compression suture), and 2 a uterus-sparing surgical procedure plus hysterectomy. In the placebo group, 3 women underwent arterial embolization, 3 a uterus-sparing surgical procedure, and 1 a hysterectomy.

†† Preoperative hematocrit was defined as the most recent hematocrit measured in the 8 days before delivery, and postoperative hematocrit was defined as the measurement closest to day 2. For patients who received a transfusion before the blood sample was obtained, the value of the postoperative hematocrit was calculated as the hematocrit at day 2 (%)-(3 × number of units of red cells transfused). Preoperative hematocrit was measured at a mean (±SD) of 38.8±1.6 weeks of gestation in the tranexamic acid group and at 38.9±1.6 weeks in the placebo group. Postoperative hematocrit was measured on day 2 in 1959 women (88.6%) in the tranexamic acid and in 1932 women (87.9%) in the placebo group and on day 1 or day 3 in 251 (11.4%) and 266 (12.1%), respectively (details are provided in Table S2).

††† Preoperative hemoglobin was defined as the most recent hemoglobin level measured in the 8 days before delivery, and postpartum hemoglobin was defined as the measurement closest to day 2. For patients who received a transfusion before the blood sample was obtained, the value of the postpartum hemoglobin was calculated as the value of the hemoglobin at day 2 (in grams per deciliter) – (1 × number of units of red cells transfused) (details are provided in Table S2).

primary outcome according to the timing of the cesarean delivery (before or during labor) and the women's postpartum hemorrhage risk status, a composite binary variable (at risk or not at risk), with risk defined as the presence of one or more of the following risk factors shown in the literature to have an odds ratio of at least 3³²: previous postpartum hemorrhage, pregnancy-related hypertensive disorder, multiple pregnancy, and cesarean delivery performed during labor.

Given the many secondary outcomes and populations analyzed and to avoid inflation of the type I error risk due to multiple comparisons, we prespecified outcomes for which a statistical comparison would be conducted and those for which only the association estimate and its 95% confidence interval would be reported (Table S3). P values were also corrected for multiple comparisons with the Benjamini–Hochberg procedure,³³ to control the false discovery rate at 0.05 within each of three subgroups for the assessment of the effect of tranexamic acid on postpartum blood loss, safety, and women's satisfaction. All statistical analyses were conducted with SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL POPULATION

From March 2018 through January 2020, we enrolled 4551 eligible participants and randomly assigned them to receive tranexamic acid (2276 women) or placebo (2275); 112 women were excluded because they withdrew consent or were found to be ineligible after randomization. Of the remaining 4439 women (intention-to-treat population), 8 had a vaginal delivery; therefore, the modified intention-to-treat population included 4431 women (2222 in the tranexamic acid group and 2209 in the placebo group) (Fig. 1). The baseline characteristics of the women, protocol adherence, and other aspects of management of the third stage of labor were similar in the two groups (Tables 1 and S4).

PRIMARY OUTCOME

Data on the primary outcome were missing for 136 women in the tranexamic acid group and for 142 in the placebo group because preopera-

tive or postoperative hematocrit or maternal weight was not available. Postpartum hemorrhage, defined as a calculated estimated blood loss greater than 1000 ml or red-cell transfusion by day 2, occurred in 556 of 2086 women (26.7%) in the tranexamic acid group and in 653 of 2067 (31.6%) in the placebo group (adjusted risk ratio, 0.84; 95% confidence interval [CI], 0.75 to 0.94; $P=0.003$ with multiple imputation of missing values) (Table 2). Sensitivity analyses with missing values imputed as failures and with complete cases yielded similar results (Table S5).

Figure 2 shows the results of the subgroup analyses. There was no evidence of differential effects of tranexamic acid according to the timing of cesarean delivery (before or during labor) or the presence or absence of known risk factors for postpartum hemorrhage.

SECONDARY OUTCOMES

There were no significant between-group differences in the incidence of any of the following hemorrhage-related clinical outcomes: mean gravimetrically estimated blood loss, provider-assessed clinically significant hemorrhage, use of additional uterotonic agents for excessive bleeding, postpartum blood transfusion, and arterial embolization or emergency surgery. However, the mean calculated estimated blood loss and mean peripartum changes in hemoglobin and hematocrit were lower in the tranexamic acid group than in the placebo group (adjusted $P<0.001$ for

all three comparisons) (Tables 2 and S6). No significant between-group differences were observed for systolic, mean, or diastolic blood pressure after delivery (Fig. S1).

ADVERSE EVENTS

Table 3 shows safety-related outcomes (additional details are provided in Tables S7 and S8). The incidence of vomiting or nausea in the operating room or PACU was higher in the tranexamic acid group than in the placebo group (43.0% vs. 36.3%, adjusted $P<0.001$). There were no significant between-group differences in prothrombin time, activated partial thromboplastin time, aminotransferase levels, fibrinogen level, or kidney-function tests on day 2. At 3 months after delivery, data on adverse events were available for 94.0% of the women. During this period, thromboembolic events had occurred in 0.4% (8 of 2049) of the women in the safety population who received tranexamic acid and in 0.1% (2 of 2056) of those who received placebo (adjusted risk ratio, 4.01; 95% CI, 0.85 to 18.92; $P=0.08$).

MATERNAL SATISFACTION, PSYCHOLOGICAL STATUS, AND PER-PROTOCOL ANALYSES

There was no evidence of differences between the groups in maternal satisfaction at day 2 and EPDS scores at 2 months (Tables S9 and S10). Analyses of the primary and secondary outcomes in the per-protocol populations showed results similar to those in the modified intention-to-treat population (Tables S11 through S14).

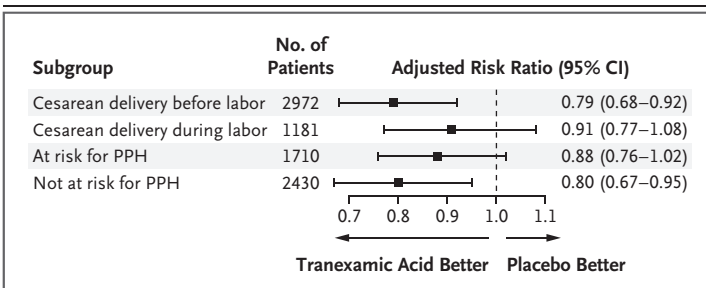


Figure 2. Prespecified Subgroup Analyses of the Primary Outcome (Modified Intention-to-Treat Population).

Shown is the risk ratio for postpartum hemorrhage (PPH) (tranexamic acid vs. placebo), adjusted for randomization stratification variables (center and timing of the cesarean delivery). PPH was defined as a calculated estimated blood loss greater than 1000 ml or receipt of a red-cell transfusion within 2 days after delivery. Women who were at risk for PPH were defined as those who had one or more risk factors for PPH with an odds ratio of at least 3 in the literature³²: previous PPH, pregnancy-related hypertensive disorder, multiple pregnancy, or cesarean delivery during labor.

DISCUSSION

Among women who underwent cesarean delivery and received a prophylactic uterotonic agent, the use of tranexamic acid resulted in a significantly lower incidence of the primary outcome — calculated estimated blood loss greater than 1000 ml or red-cell transfusion by day 2 — than did the use of placebo. However, the use of tranexamic acid did not result in lower incidences of clinical secondary outcomes related to blood loss than placebo.

Our results show that prophylactic use of tranexamic acid at cesarean delivery had a biologic effect, in that the calculated estimated blood loss was significantly lower among women who received the drug than among those who received placebo (the mean between-group difference

Table 3. Adverse Events (Safety Population).*

Event or Measure	Tranexamic Acid Group (N = 2190)	Placebo Group (N = 2177)	Unadjusted Difference (95% CI)†	Adjusted Risk Ratio or Mean Difference (95% CI)‡	P Value	
					Unadjusted	Adjusted§
In the operating room or PACU						
Vomiting or nausea — no. (%)	940/2186 (43.0)	786/2166 (36.3)	6.7 (3.8 to 9.6)	1.19 (1.08 to 1.30)	<0.001	0.001
Photopsia — no. (%)¶	8/2186 (0.4)	2/2166 (0.1)	0.3 (0.0 to 0.6)	3.92 (0.83 to 18.45)	—	—
Dizziness — no. (%)	93/2186 (4.3)	68/2166 (3.1)	1.1 (0.0 to 2.2)	1.35 (0.99 to 1.85)	—	—
Day 2 after delivery 						
Urea nitrogen — mmol/liter	3.5±1.6	3.5±1.5	0.0 (−0.1 to 0.1)	0.03 (−0.06 to 0.13)	0.47	NS
Creatinine — μmol/liter	55.1±12.1	55.6±11.3	−0.5 (−1.2 to 0.3)	−0.41 (−1.11 to 0.30)	0.26	NS
Alanine aminotransferase >2× ULN — no. (%)	26/2042 (1.3)	19/2043 (0.9)	0.3 (−0.3 to 1.0)	1.37 (0.76 to 2.48)	0.29	NS
Aspartate aminotransferase >2× ULN — no. (%)	32/2047 (1.6)	34/2039 (1.7)	−0.1 (−0.9 to 0.7)	0.94 (0.58 to 1.52)	0.79	NS
Up to 3 mo after delivery						
Completed interviews at 3 mo — no. (%)	2047/2190 (93.5)	2056/2177 (94.4)	—	—	—	—
Deep-vein thrombosis or pulmonary embolism — no. (%)**	8/2049 (0.4)††	2/2056 (0.1)	0.3 (0.0 to 0.6)	4.01 (0.85 to 18.92)	0.08	NS
Seizure — no. (%)‡‡	1/2047 (<0.1)	1/2054 (<0.1)	—	—	—	—

* Plus-minus values are means ±SD. The safety population included 2190 women who received tranexamic acid (2187 who had been randomly assigned to the tranexamic acid group and 3 who had been randomly assigned to the placebo group) and 2177 women who received placebo (2 who had been randomly assigned to the tranexamic acid group and 2175 who had been randomly assigned to the placebo group). No retinal vascular occlusion, myocardial infarction, or kidney failure treated with dialysis occurred in either group. PACU denotes postanesthesia care unit, and ULN upper limit of the normal range.

† Differences between percentages are presented in percentage points, and differences between mean values are given in the units of the mean values.

‡ Adjusted risk ratios and adjusted mean differences were estimated with the use of Poisson mixed-effects regression models and linear mixed-effects models, respectively, with systematic adjustment for randomization stratification variables (center and timing of cesarean delivery [before or during labor]).

§ P values were adjusted for multiple testing with the use of the Benjamini–Hochberg procedure; the secondary outcomes are listed in a logical order for clinicians and not in the order of the P values obtained through the Benjamini–Hochberg procedure (details are provided in Table S7). No P values are provided for outcomes for which the difference was not tested in accordance with the statistical analysis plan.

¶ Photopsia is the sensation of seeing lights, sparks, or colors.

|| If no blood sample was available at day 2, blood measures were assessed from a day 3 blood sample, if available. If no blood sample was available from day 2 or 3, blood measures were assessed from a day 1 blood sample, if available. Data on the urea nitrogen level at postpartum day 2 were not available for 160 women in the tranexamic acid group and 170 women in the placebo group, and data on creatinine at postpartum day 2 were not available for 173 women and 182 women, respectively.

** In the tranexamic acid group, 7 women had pelvic-vein thromboses (ovarian vein in all cases), and 1 a central venous catheter in the internal jugular vein and subsequent thrombosis of this catheterized vein. In the placebo group, 1 woman had a pulmonary embolism and pelvic-vein thrombosis (left ovarian and renal veins), and 1 a deep-vein thrombosis in both legs.

†† The denominator (2049) differs from the numerator of the item “Completed interviews at 3 months” (2047) because 2 women had deep-vein thrombosis during the delivery hospitalization but did not complete the interview at 3 months.

‡‡ In the tranexamic acid group, 1 woman with preexisting diabetes mellitus treated with insulin-pump therapy had seizures at postpartum day 2 in the context of severe hypoglycemia. In the placebo group, 1 woman who had severe immediate postpartum hemorrhage had seizures at postpartum day 12. The clinical examinations, computed tomographic scans of the head, and electroencephalograms were normal in both women, and they received no additional treatment.

was approximately 100 ml); this difference resulted from a significantly smaller decrease in hematocrit from before surgery to after surgery in the tranexamic acid group than in the placebo group. Nonetheless, the clinical relevance of this narrow difference is questionable since there were no significant between-group differences in the secondary clinical outcomes. Our results contrast with findings of meta-analyses of summary data from small, single-center, randomized trials, which have shown that tranexamic acid administration at cesarean delivery resulted in significantly less mean gravimetrically estimated blood loss, as well as in less frequent blood loss exceeding 500 ml and 1000 ml, less frequent use of additional uterotonic agents, and less frequent transfusions than placebo or no treatment (45 to 75% lower risk with tranexamic acid).³⁴⁻³⁷ Nonetheless, meta-analyses of small trials are prone to biases, especially publication bias; positive findings in small trials are often not substantiated by subsequent large, randomized trials.³⁸

As in the first TRAAP trial¹⁵ and in meta-analyses of randomized trials involving women undergoing cesarean delivery,^{34,35,37} nausea or vomiting occurred significantly more frequently in the tranexamic acid group than in the placebo group. As in these previous trials, the incidence of thromboembolic events during the 3 months after delivery did not differ significantly between the groups, but these events were uncommon, and power to detect differences was limited; the point estimate of the adjusted risk ratio and its 95% confidence interval (4.01; 95% CI, 0.85 to 18.92) are consistent with a wide range of plausible differences in the incidence of venous thromboembolic events, ranging from 15% lower to 18.92 times higher. This finding calls for caution, given the recent report of a significant, almost doubled risk of these events associated with tranexamic acid (with 4 g given over a period of 24 hours, a higher dose and longer duration than were used in our trial) in patients with gastrointestinal bleeding.³⁹

Our trial included a large population of women who underwent cesarean delivery, and one third of these procedures were performed during labor; our trial also had few exclusion criteria. The results are thus likely to be generalizable to women who undergo cesarean delivery in a similar context of care. Blood loss for

the primary outcome was assessed with an objective, validated calculation that was based on postoperative and preoperative hematocrit; the latter value was measured at most 8 days before delivery in order to standardize the timing of measurement and avoid heterogeneity due to possible third-trimester changes. The calculated volume of blood loss was similar to the gravimetrically estimated volume of blood loss in both groups. We excluded women who had hemoglobin levels below 9 g per deciliter to reduce the likelihood of postpartum transfusion in the absence of clinically significant blood loss.

This trial had some limitations. It was not powered to detect potentially meaningful differences in the risk of severe maternal complications, such as transfusion. The incidence of the primary outcome was twice as high as expected, a finding that may be related to the inclusion of cesarean deliveries performed during labor. One quarter of the women did not receive tranexamic acid or placebo within the 3 minutes after delivery as specified in our protocol. The per-protocol analyses provided results similar to those in the intention-to-treat analyses, although they are subject to bias because these analyses do not reflect a comparison of randomized groups. Although maternal satisfaction at day 2 and psychological status at 2 months were assessed, more subtle health dimensions, such as quality of life or mother–infant relationship, were not explored.

Among women who underwent cesarean delivery and received a prophylactic uterotonic agent, tranexamic acid administration resulted in a significantly lower incidence of calculated estimated postpartum blood loss greater than 1000 ml or red-cell transfusion by day 2 than placebo but did not result in significantly less common blood loss–related secondary clinical outcomes.

Supported by a grant from the French Ministry of Health under its Clinical Research Hospital Program (PHRC-15-0011).

Dr. Sentilhes reports receiving lecture fees from Bayer, Glaxo-SmithKline, and Sigvaris and lecture fees and consulting fees from Ferring Pharmaceuticals; Dr. Haddad, receiving consulting fees from Roche Diagnostics France; and Dr. Daniel, receiving consulting fees from LFB Biomedicaments. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the women who participated in the trial; the staff from the participating maternity units: Angers University Hospi-

tal, Bicêtre University Hospital, Besançon University Hospital, Bordeaux University Hospital, Caen University Hospital, Centre Hospitalier Inter-Communal de Créteil University Hospital, Clermont-Ferrand University Hospital, Marseille Saint Joseph Hospital, Marseille University Hospital, Montpellier University Hospital, Nancy University Hospital, Nantes University Hospital, Nîmes University Hospital, Necker-Enfants Malades Hospital, Paris Saint Joseph Hospital, Poissy/Saint-Germain Hospital, Port-Royal Maternity University Hospital, Pau Hospital, Rennes University Hospital, Robert Debré University Hospital, Rouen University Hospital, Saint-Etienne University Hospital, Schiltigheim University Hospital, Strasbourg University Hospital, Tours Uni-

versity Hospital, Toulouse University Hospital, and Trousseau University Hospital; the members of the independent safety monitoring committee: Cyril Huissoud (chair), Sophie Alexander, Hawa Keita-Meyer, and Sophie Gautier; the clinical research assistants, particularly Aurélie Darmaillacq, Aline Bibes, Melissa Charvet, Fatima-Zahra Makhoukhi, Laure Estève, and Elodie Labbé, as well as the members of the Department of Clinical Research and Innovation of the Bordeaux University Hospital who worked on this trial (Jérôme Galet, Bellabes Ghezoull, Sébastien Marchi, Anne Gimbert, and Jonathan Belcastro); and Jo Ann Cahn for her help in editing an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: Loïc Sentilhes, M.D., Ph.D., Marie V. Sénat, M.D., Ph.D., Maëla Le Lous, M.D., Norbert Winer, M.D., Ph.D., Patrick Rozenberg, M.D., Ph.D., Gilles Kayem, M.D., Ph.D., Eric Verspyck, M.D., Ph.D., Florent Fuchs, M.D., Ph.D., Elie Azria, M.D., Ph.D., Denis Gallot, M.D., Ph.D., Diane Korb, M.D., Raoul Desbrière, M.D., Camille Le Ray, M.D., Ph.D., Céline Chauleur, M.D., Ph.D., Fanny de Marcillac, M.D., Franck Perrotin, M.D., Ph.D., Olivier Parant, M.D., Laurent J. Salomon, M.D., Ph.D., Emilie Gauchotte, M.D., Florence Bretelle, M.D., Ph.D., Nicolas Sananès, M.D., Ph.D., Caroline Bohec, M.D., Nicolas Mottet, M.D., Ph.D., Guillaume Legendre, M.D., Ph.D., Vincent Letouzey, M.D., Ph.D., Bassam Haddad, M.D., Ph.D., Delphine Vardon, M.D., Hugo Madar, M.D., Aurélien Mattuizzi, M.D., Valérie Daniel, Pharm.D., Sophie Regueme, Ph.D., Caroline Roussillon, M.D., Antoine Benard, M.D., Ph.D., Aurore Georget, M.Sc., Astrid Darsonval, Pharm.D., and Catherine Deneux-Tharoux, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Obstetrics and Gynecology (L.S., H.M., A.M.), the Department of Clinical Research and Innovation (S.R.), and the Euclid-French Clinical Research Infrastructure Network (F-CRIN) Clinical Trials Platform, Department of Clinical Research and Innovation (C.R.), Bordeaux University Hospital, and the Public Health Department, Clinical Epidemiology Unit, Centre Hospitalier Universitaire (CHU) Bordeaux (A.B., A.G.), Bordeaux, the Department of Obstetrics and Gynecology, Bicêtre University Hospital (M.V.S.), the Department of Obstetrics and Gynecology, Trousseau Hospital (G.K.), the Department of Obstetrics and Gynecology, Robert Debré Hospital (D.K.), Port Royal Maternity Unit, Cochin Hospital (C.L.R.), and the Department of Obstetrics and Gynecology, Necker-Enfants Malades Hospital (L.J.S.), Assistance Publique-Hôpitaux de Paris, Université de Paris, Center of Research in Epidemiology and Statistics Sorbonne, Obstetrical, Perinatal, and Pediatric Epidemiology Research Team (EPOPÉ), INSERM, Institut National de la Recherche Agronomique (INRA), University Hospital Department-Risks in Pregnancy (G.K., E.A., C.L.R., C.D.-T.), and the Maternity Unit, Paris Saint Joseph Hospital, Paris Descartes University (E.A.), Paris, the Department of Obstetrics and Gynecology, Rennes University Hospital, Rennes (M.L.L.), the Department of Obstetrics and Gynecology, University Medical Center of Nantes, Centre d'Investigation Clinique Mère Enfant, University Hospital, and INRA, Unité Mixte de Recherche (UMR) 1280, Physiology of Nutritional Adaptations, University of Nantes, Institut des Maladies de l'Appareil Digestif, and Centre de Recherche en Nutrition Humaine-Ouest, Nantes (N.W.), the Department of Obstetrics and Gynecology, Poissy/Saint-Germain Hospital, Poissy (P.R.), the Department of Obstetrics and Gynecology, Rouen University Hospital, Rouen (E.V.), the Department of Obstetrics and Gynecology, Montpellier University Hospital, Montpellier (F.F.), INSERM, Center for Research in Epidemiology and Population Health, Unité 1018, Reproduction and Child Development, Villejuif (F.F.), the Department of Obstetrics and Gynecology, Clermont-Ferrand University Hospital, Clermont-Ferrand (D.G.), the Department of Obstetrics and Gynecology, Saint-Joseph Hospital (R.D.), and the Department of Obstetrics and Gynecology, Assistance Publique-Hôpitaux de Marseille, Aix Marseille Université (F.B.), Marseille, the Department of Obstetrics and Gynecology, Saint-Etienne University Hospital, Saint Etienne (C.C.), the Department of Obstetrics and Gynecology, University Hospital of Strasbourg, Strasbourg (F.M.), the Department of Obstetrics and Gynecology, Tours University Hospital, Tours (F.P.), the Department of Obstetrics and Gynecology, Toulouse University Hospital, Toulouse (O.P.), the Department of Obstetrics and Gynecology, Nancy University Hospital, Nancy (E.G.), the Department of Obstetrics and Gynecology, Centre Médico-chirurgical et Obstétrical, Schiltigheim (N.S.), the Department of Obstetrics and Gynecology, François Mitterrand Hospital, Pau (C.B.), the Department of Obstetrics and Gynecology, Besançon University Hospital, Besançon (N.M.), the Departments of Obstetrics and Gynecology (G.L.) and Pharmacy (V.D., A.D.), Angers University Hospital, Angers, the Department of Obstetrics and Gynecology, Carêmeau University Hospital, Nîmes (V.L.), the Department of Obstetrics and Gynecology and Reproductive Medicine, University Paris Est Créteil, Centre Hospitalier Inter-Communal de Créteil, Créteil (B.H.), the Department of Obstetrics and Gynecology, Caen University Hospital, Caen (D.V.), and PPRIGO (Production Pharmaceutique pour la Recherche Institutionnelle du Grand Ouest), Brest University Hospital, Brest (V.D., A.D.) — all in France.

REFERENCES

- Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health* 2014;2(6):e323-e333.
- Gallos I, Williams H, Price M, et al. Uterotonic drugs to prevent postpartum haemorrhage: a network meta-analysis. *Health Technol Assess* 2019;23:1-356.
- Sentilhes L, Goffinet F, Vayssière C, Deneux-Tharoux C. Comparison of postpartum haemorrhage guidelines: discrepancies underline our lack of knowledge. *BJOG* 2017;124:718-22.
- Sentilhes L, Merlot B, Madar H, Sztark F, Brun S, Deneux-Tharoux C. Postpartum haemorrhage: prevention and treatment. *Expert Rev Hematol* 2016;9:1043-61.
- Sentilhes L, Lasocki S, Ducloy-Bouthors AS, et al. Tranexamic acid for the prevention and treatment of postpartum haemorrhage. *Br J Anaesth* 2015;114:576-87.
- Sentilhes L, Madar H, Mattuizzi A, et al. Tranexamic acid for childbirth: why, when, and for whom. *Expert Rev Hematol* 2019;12:753-61.
- Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;344:e3054.
- Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med* 2017;376:136-48.
- The CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised,

- placebo-controlled trial. *Lancet* 2010;376:23-32.
10. The CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet* 2019;394:1713-23.
 11. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with postpartum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:2105-16.
 12. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. Geneva: World Health Organization, 2017 (<https://apps.who.int/iris/bitstream/handle/10665/259374/9789241550154-eng.pdf>).
 13. Committee on Practice Bulletins-Obstetrics. Practice bulletin no. 183: postpartum hemorrhage. *Obstet Gynecol* 2017;130(4):e168-e186.
 14. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F-X, Roberts I. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet* 2018;391:125-32.
 15. Sentilhes L, Winer N, Azria E, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. *N Engl J Med* 2018;379:731-42.
 16. Ker K, Shakur H, Roberts I. Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials. *BJOG* 2016;123:1745-52.
 17. Sentilhes L, Brun S, Madar H, Deneux-Tharaux C. Tranexamic acid for preventing postpartum blood loss at cesarean delivery: is evidence sufficient? *Acta Obstet Gynecol Scand* 2016;95:836.
 18. Sentilhes L, Daniel V, Darsonval A, et al. Study protocol. TRAAP — TRANexamic Acid for Preventing postpartum hemorrhage after vaginal delivery: a multicenter randomized, double-blind, placebo-controlled trial. *BMC Pregnancy Childbirth* 2015;15:135.
 19. Sentilhes L, Daniel V, Deneux-Tharaux C. TRAAP2 — TRANexamic Acid for Preventing postpartum hemorrhage after cesarean delivery: a multicenter randomized, double-blind, placebo-controlled trial — a study protocol. *BMC Pregnancy Childbirth* 2020;20:63.
 20. Sentilhes L, Vayssière C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol* 2016;198:12-21.
 21. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MSV. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med* 2014;370:1307-15.
 22. Sheehan SR, Montgomery AA, Carey M, et al. Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective caesarean section: double blind, placebo controlled, randomised trial. *BMJ* 2011;343:d4661.
 23. Carvalho JCA, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective cesarean delivery: a dose-finding study. *Obstet Gynecol* 2004;104:1005-10.
 24. Shook PR, Schultz JR, Reynolds JD, Spahn TE, DeBalli P. Estimating blood loss for cesarean section: how accurate are we? *Anesthesiology* 2003;98:Suppl 1:8. abstract.
 25. Maged AM, Helal OM, Elsherbini MM, et al. A randomized placebo-controlled trial of preoperative tranexamic acid among women undergoing elective cesarean delivery. *Int J Gynaecol Obstet* 2015;131:265-8.
 26. Gai M, Wu L, Su Q, Tatsumoto K. Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial. *Eur J Obstet Gynecol Reprod Biol* 2004;112:154-7.
 27. Movafegh A, Eslamian L, Dorabadi A. Effect of intravenous tranexamic acid administration on blood loss during and after cesarean delivery. *Int J Gynaecol Obstet* 2011;115:224-6.
 28. Xu J, Gao W, Ju Y. Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: a double-blind randomized trial. *Arch Gynecol Obstet* 2013;287:463-8.
 29. Guedeney N, Fermanian J. Validation study of the French version of the Edinburgh Postnatal Depression Scale (EPDS): new results about use and psychometric properties. *Eur Psychiatry* 1998;13:83-9.
 30. Meher S, Cuthbert A, Kirkham JJ, et al. Core outcome sets for prevention and treatment of postpartum haemorrhage: an international Delphi consensus study. *BJOG* 2019;126:83-93.
 31. Misme H, Dupont C, Cortet M, Rudigoz R-C, Huissoud C. Analyse descriptive du volume des pertes sanguines au cours de l'accouchement par voie basse et par césarienne. *J Gynecol Obstet Biol Reprod (Paris)* 2016;45:71-9.
 32. Postpartum haemorrhage, prevention and management (Green-top Guideline No. 52). London: Royal College of Obstetricians and Gynaecologists, 2009.
 33. Yoav B, Yosef H. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 1995;57:289-300.
 34. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* 2015;(6):CD007872.
 35. Alam A, Choi S. Prophylactic use of tranexamic acid for postpartum bleeding outcomes: a systematic review and meta-analysis of randomized controlled trials. *Transfus Med Rev* 2015;29:231-41.
 36. Simonazzi G, Bisulli M, Saccone G, Moro E, Marshall A, Berghella V. Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials. *Acta Obstet Gynecol Scand* 2016;95:28-37.
 37. Li C, Gong Y, Dong L, Xie B, Dai Z. Is prophylactic tranexamic acid administration effective and safe for postpartum hemorrhage prevention? A systematic review and meta-analysis. *Medicine (Baltimore)* 2017;96(1):e5653.
 38. Sivakumar H, Peyton PJ. Poor agreement in significant findings between meta-analyses and subsequent large randomized trials in perioperative medicine. *Br J Anaesth* 2016;117:431-41.
 39. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomized, double-blind, placebo-controlled trial. *Lancet* 2020;395:1927-36.

Copyright © 2021 Massachusetts Medical Society.